Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Joint Gastrointestinal Drugs Advisory Committee and the Drug Safety and Risk Management Drugs Advisory Committee Meeting

December 9, 2013

Location: FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Rm. 1503), Silver Spring, MD

Topic: The committee discussed two biologics license applications (BLA) for vedolizumab injection (proposed tradename Entyvio) submitted by Takeda Pharmaceuticals, U.S.A., Inc. BLA 125476 proposes an indication for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to, have lost response to, or were intolerant to either conventional therapy or a tumor necrosis factor-alpha (TNFα) antagonist. BLA 125507 proposes an indication for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response to, have lost response to, or were intolerant to either conventional therapy or a TNFα antagonist.

These summary minutes for the December 9, 2013 joint meeting of the Gastrointestinal Drugs Advisory Committee and the Drug Safety and Risk Management Drugs Advisory Committee of the Food and Drug Administration were approved on January 31, 2014.

I certify that I attended the December 9, 2013 joint meeting of the Gastrointestinal Drugs Advisory Committee and the Drug Safety and Risk Management Drugs Advisory Committee and that these minutes accurately reflect what transpired.

_____/s/_____
Cindy Hong, Pharm.D.
Designated Federal Officer
Gastrointestinal Drugs
Advisory Committee (GIDAC)

_____/s/_____
Steve Solga, MD
Chairperson, GIDAC

Summary Minutes of the Joint Gastrointestinal Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee Meeting

The following is the final report of the joint meeting of the Gastrointestinal Drugs Advisory Committee (GIDAC) and the Drug Safety and Risk Management (DSaRM) Advisory Committee held on December 9, 2013. A verbatim transcript will be available in approximately six weeks, sent to the Division of Gastroenterology and Inborn Errors Products and Office of Surveillance and Epidemiology, and posted on the FDA website at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/GastrointestinalDrugsAdvisoryCommittee/ucm371061.htm and http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm332858.htm

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

The Gastrointestinal Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee of the Center for Drug Evaluation and Research met on December 9, 2013 from 10:30 a.m. to 6:00 p.m. at the FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Rm. 1503), Silver Spring, MD. Prior to the meeting, members and temporary voting members were provided copies of the background material from the FDA and Takeda Pharmaceuticals, USA Inc. The meeting was called to order by Steve Solga, MD (Chairperson); the conflict of interest statement was read into the record by Cindy Hong, PharmD (Designated Federal Officer). There were approximately 170 people in attendance. There were twelve Open Public Hearing speakers.

Issue: The committee discussed two biologics license applications (BLA) for vedolizumab injection (proposed tradename Entyvio) submitted by Takeda Pharmaceuticals, U.S.A., Inc. BLA 125476 proposes an indication for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to, have lost response to, or were intolerant to either conventional therapy or a tumor necrosis factor-alpha (TNFα) antagonist. BLA 125507 proposes an indication for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response to, have lost response to, or were intolerant to either conventional therapy or a TNFα antagonist.

Attendance:
GIDAC Members Present (Voting): Elizabeth Bell-Perkins, MPH (Consumer Representative), Steven Solga, MD (Chairperson), Gagan Sood, MD, Marc Wishingrad, MD *(via phone)*

GIDAC Members Not Present (Voting): Shrikant Bangdiwala, PhD, Richard Grand, MD, Amy Foxx-Orenstein, DO, Bo Shen, MD, Brennan Spiegel, MD

GIDAC Member Present (Non-Voting): Helmut Albrecht, MD, MS, FFPM (Industry Representative)

DSaRM Members Present (Voting): Tobias Gerhard, PhD, RPh, Peter Kaboli, MD, Til Stürmer, MD, MPH, PhD *(via phone)*, Maria Suarez-Almazor, MD, PhD

DSaRM Members Not Present: Brian Erstad, PharmD, Sonia Hernandez-Diaz, MD, DrPH, Karen Hopkins, MD (Consumer Representative), David Madigan, PhD, Jeanmarie Perrone, MD, FACMT, Marjorie Shaw Phillips, MS, RPh, FASHP, Andy Stergachis, PhD, RPh, Linda Tyler, PharmD, FASHP, Almut Winterstein, PhD

DSaRM Member Present (Non-Voting): Patrizia Cavazzoni, MD (Industry Representative)

Temporary Members (Voting): Matthew Chandler, MD, Scott Emerson, MD, PhD, Linda Feagins, MD *(via phone)*, Myla Goldman, MD, MSc *(via phone)*, Martin Greene, MD, David Keljo, MD, PhD, Kenneth Koch, MD *(via phone)*, Andelka LoSavio, MD *(via phone)*, Elaine Morrato, DrPH, Avindra Nath, MD, Brian Plaska (Patient Representative), Michael Rice, MD, James Sejvar, MD *(via phone)*

Speaker (Non-Voting): Eugene Major, MD

FDA Participants (Non-Voting): Julie Beitz, MD, Donna Griebel, MD, Joyce Korvick, MD, MPH, Lisa LaVange, PhD, Claudia Manzo, PharmD, Anil Rajpal, MD, MPH

Designated Federal Officer (Non-Voting): Cindy Hong, PharmD

Open Public Hearing Speakers: Maria Abreu, MD, Melody McDowall, LMSW, Sarah Murray, MD (University of California, San Francisco), Dominic Loise, March Reiss, LCSW (IBD Support Foundation), Shavon Fields, David Peura, MD, FACP, MACG, AGAF (University of Virginia Health System), Lisa Miskovsky, David Rubin, MD, FACG, AGAF, FACP (Inflammatory Bowel Disease Center), Arthur Kornbluth, MD (The Mount Sinai Medical Center), Laura Wingate (Crohn's & Colitis Foundation of America), Laura Wingate on behalf of Stacy Kane

***The agenda proceeded as follows*:**

Call to Order Introduction of Committee	**Steven Solga, MD** Committee Chairperson, GIDAC
Conflict of Interest Statement	**Cindy Hong, PharmD** Designated Federal Officer, GIDAC

Opening Remarks	**Anil Rajpal, MD, MPH** Medical Team Leader Division of Gastroenterology and Inborn Errors Products (DGIEP) Office of Drug Evaluation III (ODEIII) Office of New Drugs (OND), CDER, FDA
FDA PRESENTATION	
Natalizumab (Tysabri) Experience With Progressive Multifocal Leukoencephalopathy (PML)	**LCDR Andrew J. Fine, PharmD, BCPS** Safety Evaluator Division of Pharmacovigilance I Office of Pharmacovigilance and Epidemiology Office of Surveillance and Epidemiology (OSE) CDER, FDA
SPEAKER PRESENTATION	
JC Virus and Pathogenesis of PML	**Eugene Major, PhD** Chief Laboratory of Molecular Medicine and Neuroscience National Institute of Neurological Disorders and Stroke National Institutes of Health Bethesda, Maryland
SPONSOR PRESENTATIONS	**Takeda Pharmaceuticals**
Vedolizumab	**Colleen Costello, PhD** Senior Director, Global Regulatory Affairs Takeda Pharmaceuticals
Unmet Need and Standard of Care in Ulcerative Colitis and Crohn's Disease Vedolizumab Benefit-Risk in Ulcerative Colitis and Crohn's Disease	**Bruce Sands, MD** Dr. Burrill B. Crohn Professor of Medicine Chief, Division of Gastroenterology Icahn School of Medicine at Mount Sinai Hospital New York, New York
A Therapeutic Strategy for Specifically Targeting Gut-homing Leukocytes	**Ulrich von Andrian, MD** Mallinckrodt Professor of Immunopathology Division of Immunology Harvard Medical School Boston, Massachusetts

Efficacy: 1. Ulcerative Colitis 2. Crohn's Disease Vedolizumab Safety: 1. Ulcerative Colitis 2. Crohn's Disease	**Asit Parikh, MD, PhD** Vice President, Gastroenterology and General Medicines R&D Takeda Pharmaceuticals
An Assessment of the Risk of PML with Vedolizumab	**Joseph Berger, MD** Ruth L. Works Professor Director of the MS Center University of Kentucky College of Medicine Lexington, Kentucky
Vedolizumab Risk Management Program	**Lesley Wise, PhD** Vice President, Global Pharmacovigilance Risk Management and Pharmacoepidemiology Takeda Pharmaceuticals

LUNCH

Clarifying Questions to the Presenters

FDA PRESENTATIONS

Crohn's Disease Efficacy: Statistical Considerations	**Freda W. Cooner, PhD** Acting Statistics Team Leader Division of Biometrics III Office of Biostatistics Office of Translational Sciences, CDER, FDA
Crohn's Disease Efficacy: Clinical Considerations	**Klaus Gottlieb, MD, MS, MBA** Medical Reviewer DGIEP, ODEIII, OND, CDER, FDA
Vedolizumab Clinical Trial Safety and Approach to Risk Assessment	**Laurie Muldowney, MD** Medical Reviewer DGIEP, ODEIII, OND, CDER, FDA
Risk Management Considerations	**George Neyarapally, PharmD, MPH** Risk Management Analyst Division of Risk Management Office of Medication Error Prevention and Risk Management, OSE, CDER, FDA

Clarifying Questions to the Presenters

BREAK

Open Public Hearing

Questions to the Committee and Committee Discussion

BREAK

Questions to the Committee and Committee Discussion (cont.)

ADJOURNMENT

Questions to the Committee:

Efficacy in Crohn's Disease (CD):

1. Evidence for vedolizumab efficacy for CD induction is provided by one trial but not supported by a second trial that primarily enrolled a refractory population. Evidence for vedolizumab efficacy for CD maintenance is provided in one trial.

   a. **VOTE**: Do the available data support the efficacy of vedolizumab for the proposed CD induction indication? (please explain your vote)

      Vote: YES = 12 NO = 9 ABSTAIN = 0

      Committee Discussion: *The majority of the committee voted that the data support the efficacy of vedolizumab for the proposed CD induction indication and noted that the 10 week data were convincing. Those voting "No" commented that the data presented by FDA showed that only one primary endpoint was met and the totality of the data did not meet the threshold to support the efficacy for induction. Please see the transcript for details of the committee discussion.*

   b. **VOTE**: Do the available data support the efficacy of vedolizumab for the proposed CD maintenance indication? (please explain your vote)

      Vote: YES = 19 NO = 1 ABSTAIN = 1
      Committee Discussion: *The committee agreed that the available data support the efficacy of vedolizumab for the proposed CD maintenance indication. The committee member who abstained stated that he abstained from voting due to his lack of knowledge of how the issues with the drug during induction would affect the maintenance. One member who had originally voted "No" subsequently noted during the explanation of the vote that she wanted to vote "Yes." Please see the transcript for details of the committee discussion*

c. **DISCUSSION:** Please discuss if further studies are needed and what those studies should address.

Committee Discussion: *Committee members commented that the demand for other treatments for CD is high and additional trials would increase cost and delay the drug availability. Please see the transcript for details of the committee discussion*

Safety:

2. **VOTE:** Considering the currently available nonclinical and clinical data, has the applicant adequately characterized the potential risk of PML with vedolizumab to support approval? (please explain your vote)

Vote: YES = 21 NO = 0 ABSTAIN = 0

Committee Discussion: *The committee agreed that the applicant has adequately characterized the potential risk of PML with vedolizumab with the current data to support approval. Members noted that continued monitoring and observation are still necessary to assess the potential risk of PML and the occurrence of serious infections. Please see the transcript for details of the committee discussion*

3. **VOTE:** If vedolizumab is approved, should concomitant immunosuppressants be limited to a specific duration (e.g., during induction only)? (please explain your vote)

Vote: YES = 1 NO = 19 ABSTAIN = 1

Committee Discussion: *The committee agreed that concomitant immunosuppresants should not be limited to a specific duration. The member who voted "Yes" commented that she wants to make sure that there was language in the labeling that reflects what was done in the clinical program. The member who "Abstained" noted that he hopes there is no restriction and would like to see how the drug is used in real practice. Please see the transcript for details of the committee discussion.*

Benefit-Risk Assessment for UC:

4. **VOTE (choose a, b, or c):** Based on currently available efficacy and safety data, do the benefits outweigh the potential risks of vedolizumab (in particular, PML) to support approval for:
   a. the proposed UC population that have failed steroids or immunosuppressants or TNFα-antagonists?
   b. patients that have failed immunosuppressants or TNFα-antagonists (i.e., the indicated population would not include patients that failed steroids only)?
   c. neither a nor b.

Vote: A = 13 B = 8 C = 0

Committee Discussion: *The majority of the members agreed that the benefits outweigh the potential risks of vedolizumab to support the approval for the proposed UC population that have failed steroids or immunosuppressants or TNF α-antagonists, and commented that restrictions would be burdensome in clinical practice. The Members who voted for "B" noted that patients failing steroids have other options. One member who had originally voted for "B" subsequently noted during the explanation of the vote that he wanted to vote for "A." Please see the transcript for details of the committee discussion*

Benefit-Risk Assessment for CD:

5. **VOTE (choose a, b, or c):** Based on currently available efficacy and safety data, do the benefits outweigh the potential risks of vedolizumab (in particular, PML) to support approval for:
   a. the proposed CD population that have failed steroids or immunosuppressants or TNFα-antagonists?
   b. patients that have failed immunosuppressants or TNFα-antagonists (i.e., the indicated population would not include patients that failed steroids only)?
   c. neither a nor b.

Vote: ***A = 14*** ***B = 6*** ***C = 1***

Committee Discussion: *The majority of the committee agreed that the benefits outweigh the potential risks of vedolizumab to support approval for the proposed CD population that have failed steroids or immunosuppressants or TNFα-antagonists for the same reasons as the UC indication. Those who voted for "B" noted that the margin between risk and benefit in this population is smaller than in UC. One member who voted "C" commented that immunosuppressants and anti-TNF agents are well established and vedolizumab appears to be slow to work. Please see the transcript for details of the committee discussion*

Safety and Risk Mitigation Strategy Considerations:

6. **DISCUSSION:** If vedolizumab is approved for the proposed UC or CD indications:

   a. Discuss what post-market risk mitigation strategies beyond labeling, if any, would be needed to ensure that the product's benefits outweigh its risks.
   b. Discuss what additional safety studies or trials should be conducted, if any.

Committee Discussion: *The committee members commented that it is important to quantify PML risk and to monitor other infections in addition to PML. The committee also noted that post-market risk mitigation strategies should not be burdensome for the practitioners. It was also suggested that self- reported adverse events registries could also be considered. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at 6:01 p.m.